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CYTOMEGALOVIRUS INFECTIONS

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Cytomegalovirus (CMV) is a common virus belonging to the herpesvirus family. It is widely distributed and infects a large portion of the world population. Cytomegalovirus is highly species-specific, and only human strains are known to produce human disease. CMV is considered the most common infectious cause of mental retardation and congenital deafness in the United States.

Epidemiology

CMV is excreted in urine, saliva, breast milk, cervical secretions, and semen during primary or reactivated infection. Cytomegalovirus is transmitted by intimate exposure by cutaneous or mucosal contact with infectious tissues, secretions or excretions. Intimate sexual contact is also important in the transmission of CMV.

Seropositive healthy persons have latent CMV in their leukocytes and tissues; hence, blood transfusions and organ transplantation can result in viral transmission.

CMV can be transmitted from mother to child in utero during a primary infection or reactivation of the mother. Transmission may occur in utero, at birth or postnatally by ingestion of CMV-positive human milk. Approximately 1% of all live-born infants are infected in utero and excrete CMV at birth. While in utero fetal infection can occur after maternal primary infection or after reactivation of infection during pregnancy, sequelae are far more common in infants after maternal primary infection, with 10% to 20% diagnosed with mental retardation or sensorineural deafness in childhood and 5% having manifestations evident at birth. The most important source of clinically significant congenital infections is in infants born to primiparous mothers with a primary infection during pregnancy.

In day care centers, the prevalence of CMV in urine or saliva of apparently healthy children can be high, but the risk of spread of CMV infection to child care personnel, especially women in their reproductive years, is largely unknown.

Infection is common in all human populations, reaching 60 to 70% in urban U.S. cities.

The incubation period for CMV infections transmitted by contact is unknown. Clinical manifestations occur 3 to 12 weeks after an infectious blood transfusion and between 1 and 4 months after an infecting tissue transplantation.

Clinical Description

CMV has the ability to establish latent infection in the host after recovery from acute infection. The exact mechanisms controlling latency are unclear, but polymorphonuclear cells, T lymphocytes, endothelial vascular tissue, renal epithelial cells, and salivary glands may all harbor the virus in a nonreplicating or slowly replicating form. Activation from this latent state can occur after immunosuppression, other illness, or the use of chemotherapeutic agents.

Manifestations of acquired cytomegalovirus (CMV) infections vary depending on the age and immunocompetence of the host.

- Asymptomatic infections are the most common, particularly in children.
- An infectious mononucleosis-like syndrome with prolonged fever and mild hepatitis, with negative tests for infectious mononucleosis has been described in adults. About 79% of infectious mononucleosis is caused by the Epstein-Barr virus (EBV) and the other 21% is caused by acute CMV infection. The heterophile agglutinin test is negative in CMV mononucleosis and usually positive in EBV mononucleosis. A sore throat with enlarged, exudate covered tonsils is more common with EBV infection. The CMV-induced infectious mononucleosis syndrome has been termed typhoidal because the symptoms may be more systemic in nature, with fever predominating and fewer signs of enlarged lymph nodes or splenomegaly.
- Guillain Barre syndrome may accompany acute CMV mononucleosis. It presents with polyneuritis with sensory and motor weakness in the extremities. Complete recovery requires about 3 months for most patients.
- Pneumonia, colitis, meningo encephalitis, and retinitis occur in immunocompromised hosts (particularly those receiving treatment for malignant neoplasms), in human immunodeficiency virus (HIV) infected persons, or in persons receiving immunosuppressive therapy for organ transplantation.
- Congenital infections also are expressed by a spectrum of disease. Usually infection is asymptomatic, but some congenitally infected infants who appear to be asymptomatic at birth are identified in infancy or childhood as having a hearing loss or learning disability. The most severe form of disease occurs in the perinatal period, following congenital or acquired infection, especially involving the CNS and liver. Lethargy, hepatosplenomegaly, chorioretinitis, intracerebral calcifications, and pulmonary infiltrates occur in varying degrees.
- Latent CMV frequently will reactivate in immunosuppressed persons and can result in disease if the immunosuppression is severe (eg, patients with acquired immunodeficiency syndrome and solid-organ and bone marrow transplant recipients).

Fetuses, patients with debilitating diseases, those on immunosuppressive drugs, and especially organ allograft recipients (kidney, heart, bone marrow) are most susceptible to overt and severe disease. Without appropriate prophylactic measures, the seronegative recipient of an organ from a seropositive donor is at the highest risk (> 60%) of developing CMV disease.

Laboratory Tests

The following tests are an indication of actively replicating virus. This state is distinct from latent infection and is traditionally termed CMV "disease."

- Isolation of the virus in tissue culture from the urine, pharynx, peripheral blood leucocytes, human milk, semen, cervical secretions and other tissues and body fluids.
- Detection of the early matrix protein pp65, as occurs with a positive CMV "rapid antigen" test
- Detection of CMV DNA by means of polymerase chain reaction (PCR) from peripheral blood leukocytes or bodily fluid or biopsy material.

These tests indicate a recent infection

- Presence of CMV-specific IgM. The presence of IgM antibodies against CMV in cord serum is suggestive but not completely specific for congenital infection.
- Rise in antibody titers between acute and convalescent sera.
- Presence of IgG antibodies without documentation of a rise in antibody levels is an indication of past infection and probable immunity.

The state laboratory now has the capability of performing ELISA testing for IgG and IgM antibody

interpretation. (IgG indicates past infection or passively acquired maternal antibody and an immune status. IgM indicates active infection). This will provide more rapid test results and should eliminate the necessity for a second blood specimen.

Collect one red-topped tube of blood within seven (7) to ten (10) days after the onset of illness or no longer than three (3) weeks after birth. If the blood is not obtained within this time frame, a second specimen may be required. It is imperative that the lab slip indicate the onset date of the suspected case's signs and symptoms of illness or the date of birth and the time interval between then and the date of blood collection. Without this information, the lab cannot accurately interpret the laboratory results. The blood is to either be spun down and the sera sent or the whole blood sent refrigerated.

Interpretation of Laboratory Test:

IgM antibodies are the first to appear in response to an infection and usually are measurable within seven (7) to ten (10) days after antigen (virus) enters the body. These IgM antibodies normally persist for four to six weeks after onset of infection and the level falls rapidly as the IgG antibody synthesis begins; therefore, detection of IgM is indicative of a current infection. IgG antibodies may be measurable at low levels for many years and in some cases for a lifetime.

The test results will be reported as one of the following (based on the IgM value):

1. Negative for CMV-specific IgM
2. Equivocal probable negative sample. Another sample requested (will be tested for IgG)
3. Equivocal probable positive sample. Another sample requested for IgG)
4. Positive for CMV-specific IgM

Surveillance

CMV infection is not a reportable condition

Case Definition

A case of cytomegalovirus is defined as an illness characterized by clinical symptoms compatible with cytomegalovirus infection (including an infectious mononucleosis-like syndrome with prolonged fever and mild hepatitis in adults) and is laboratory confirmed by one or more methods.

Investigation

Because of the high prevalence of asymptomatic shedders in the population, investigation of individual cases is impractical and not warranted.

Screening is not indicated

A major concern caused by CMV is the potential exposure of a pregnant woman or a woman of child bearing age to the virus. Routine serologic screening for antibody to CMV in day care or health care facility workers is not recommended because the extent of risk has not been established.

A British study to determine antibody status of women who work in health care was abandoned after 18 months. If a female HCW tested negative there was no way to guarantee she wouldn't pick up CMV outside the institution anyway, particularly with her own children at home. If she tested seropositive there was no guarantee she wouldn't reactivate during pregnancy. The conclusion of the study was that screening of HCWs did not provide useful information, but only added confusion to the issue of safety when working with a known CMV excreter. Over 15 studies have been published comparing rates of CMV acquisition in HCW exposed to patients vs. unexposed. In all the rates of acquisition were 0-6/100

person-years (usually 2%), with little or no difference as a result of patient exposure. Most people become infected from their own children.

Isolation of known shedders is not recommended

Most CMV-shedding patients are unidentified. The few known shedders in a facility do not need to be placed on special precautions. No infant or child with CMV infection should be excluded from any education program for which he/she is otherwise eligible. The risk of exposure to such children should be viewed in the context of the far greater exposure to many healthy children who are unrecognized shedders of CMV.

Treatment

Ganciclovir is beneficial for treatment of retinitis caused by acquired or recurrent CMV infection in HIV-infected patients.

Prevention

- The only known effective method of reducing the risk of CMV transmission to health care workers, day care center employees and to uninfected infants is good handwashing and the avoidance of secretions. Pregnant personnel who may be in contact with CMV-infected patients should be counseled about the potential risks of acquisition and urged to practice good hygiene, particularly hand washing. Approximately 1% of infants in most newborn nurseries and a higher percentage of older children excrete CMV without clinical manifestations. Risks to the fetus are greatest during the first half of gestation.
- Pasteurization or freezing of donated human milk can reduce the likelihood of CMV transmission. If fresh donated milk is needed for infants born to CMV antibody-negative mothers, providing these infants with milk from only CMV antibody-negative women should be considered.
- CMV hyperimmune globulin has been developed for prophylaxis of disease in bone marrow transplant patients.
- Transmission of CMV by blood transfusion to preterm infants or others has been virtually eliminated by the use of CMV antibody-negative donors, by freezing red blood cells in glycerol before administration, by removal of the buffy coat, or by filtration to remove white blood cells.

Hospital precaution and isolation: Standard precautions